SCHERING CORPORATION

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August 31, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

SUBJECT: DOCKET NO. 99D-1454; COMMENTS ON DRAFT GUIDANCE FOR INDUSTRY ON NASAL SPRAY AND INHALATION SOLUTION, SUSPENSION, AND SPRAY DRUG PRODUCTS; CHEMISTRY, MANUFACTURING, AND CONTROLS DOCUMENTATION

Dear Sir/Madam:

Schering Corporation has carefully reviewed the Wednesday, June 2, 1999 Federal Register Notice, Page 29657 and the associated Draft Guidance For Industry on Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products; Chemistry, Manufacturing, and Controls Documentation. Schering Corporation is a developer, manufacturer and marketer of several Nasal Spray and Inhalation drug products. Hence, Schering Corporation is impacted by the draft guidance document.

Schering Corporation submits the following comments on the proposed guideiine:

Page/Line	Item	Discussion
3-4/105-6	Sterility of inhalation products	These types of products are made with a low bioburden and therefore should not have be manufactured as sterile. What is the rationaie of this-new proposed recommendation?
5/181-182	C. Inhalation Sprays, Ill. Drug Product, C. Specs for the Formulation Components, 1. Active Ingredient	The requirement for a specification for control of crystalline form (e.g., shape, texture, surface) of the drug substance should be deleted, These properties are subjective and adequate means to measure them do not exist.

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6/195 --	C. Inhalation Sprays, III. Drug Product C. Specs for the Formulation Components, 1. Active Ingredient	These sentences imply that if an impurity is found occasionally at a level greater thar 0.1% it need not be identified. Please clarify.
7/249-254	C. Inhalation Sprays, Ill. Drug Product, C. Specs for the Formulation Components, 2. Excipients	It seems excessive to have to test batches of each excipient using in postapprova production batches, when acceptability has already been demonstrated in stability anc production batches.
9/334-335	C. Inhalation Sprays, III. Drug Product , E. Method of Manufacturing/ Packaging	It may be impossible to demonstrate absence of something. It does seem reasonable to determine the levels of lcachables or to show that the levels are below the detection limits of the assays. Same comments for lines 659-661
10/364-367	1. Nasal Sprays, a. Appearance, color and clarity	A quantitative color test and specification is unnecessary for the drug product. In instances when color is associated with degradation, a specific impurity/degradation product test is much more sensitive and meaningful. Incorporation of a color test and specification incurs additional cost to the manufacturer, without providing any benefit.
I O/379-386	1. Nasal Sprays, c. Drug Content (Assay)	While the assay of the drug substance in the entire container may be appropriate for aerosol formulations and unit dose solutions and suspensions for inhalation, it s not appropriate for aqueous based nasal spray and multiple dose solutions and suspensions for inhalation. For the latter, the assay should be based on concentration. This, along with the net content of the formulation per container, i.e., fill volume or weight, are adequate for control of the formulation and filling process. The guidance should. be revised to make-this distinction.
11/417-474	1. Nasal Sprays, g. Spray Content Uniformity (SCU)	In light of the complexity of drug products For inhalation, a more relevant and statistically based approach to dose uniformity should be explored between industry and regulatory authorities. The

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		acceptance criteria for individual determinations of the delivered dose provided in this guidance are too tight, anc not consistent with the USP and other major pharmacopoeia. Furthermore, the requirement that no individual determination lie outside the range of 75.C to 125% of label claim is not reasonable without any recourse for re-testing. Specifications should be derived using historical data (particularly batches used in safety and efficacy trials and primary stability studies). Thus, dose content uniformity specifications should be set on a product-by-product basis rather than demanding conformance to an a *priori* set of specifications.
13/476-502	1. Nasal Sprays, i. Spray Pattern and Plume Geometry	Testing for spray pattern may be useful during the development process and for testing and release of components, e.g., actuators, nozzles, etc., but should not be required for product release.
14/5 15-523	1. Nasal Sprays, k. Particle Size Distribution	The requirement for particle size distribution should be deleted for nasal sprays. Particle sizing techniques such as cascade impaction are not applicable due to the size of the droplets in the plume. Furthermore, the presence of suspending agents in a formulation make it difficult, if not impossible, to measure the drug substance particle size distribution by visual or light, scattering methods.
15/575-576	1. Nasal Sprays, p. Net Content and Weight Loss	The sentence should be revised to read "The total net content of the formulation in the entire container should be determined."
22/851	2, Inhalation Solutions, Suspensions and Sprays, G. Container/ Closure Systems, Source and Fabricator for each part of pump	The above information is considered proprietary 'and not readily available to the drug manufacturer. It is contained- in the vendor DMF.

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22/854	2. Inhalation Solutions, Suspensions and Sprays, G. Container/ -Closure Systems, Schematic Engineering Drawings of components	Schematic engineering drawings are extremely detailed with dimensions and various radii important for moldability but not functionality. The drawings supplied should be acceptance specification drawings depicting the parameters which are routinely monitored and controlled.
22/855-856	2. Inhalation Solutions, Suspensions and Sprays, G. Container/ Closure Systems, Precise dimensional measurements of the container closure and pump components.	The amount-of data to meet this requirement will be voluminous. It will be an additional burden to both the drug manufacturer and the reviewer. Instead, the drug manufacturer should provide the specifications, drawings and test parameters with a statement that incoming components for the stability lots meet those specifications. The raw data on measurements can be made available to the FDA at the site inspection.
23/861	2. Inhalation Solutions, Suspensions and Sprays, G. Container/ Closure Systems, Acceptance criteria, test procedures, etc.	The title or description of the test procedure rather than the SOP should be provided to avoid unnecessary FDA reporting when SOP's are updated.
23/862	2. Inhalation Soiutions, Suspensions and Sprays, G. Container/ Closure Systems, Physicochemical parameters and dimensional measurements of the container closure and pump components.	"Physicochemical parameters" is vague. Physicochemical tests are specified in the USP but they are only used on a one-time basis to ensure the material meets the USP limits. "Physicochemical parameters" should be replaced by "identity tests".
24/93 l-934	2. inhalation Solutions, Suspensions and Sprays, G. Container/ Closure Systems, 3. Routine extraction	Why is it necessary to perform extactable testing on every incoming lot of container components. This seems excessive and certainly inconsistent with what is expected for parenteral products
25/946, 947	2. Inhalation Solutions, Suspensions and Sprays, G. Container/ Closure Systems, 4. Acceptance Criteria	Specifications for labels, adhesives and inks will impact current stability programs. They will need to be specified on stability, set-up and results included in stability reports. This will also require incoming

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		testing and release of these components
30/1163-1165	Section IV. Drug Product Characterization Studies	The requirement that drug product characterization studies be conducted on a minimum of three batches of drug product intended for-marketing is unreasonable. These studies are complex, labor intensive, and lengthy. Relevant information can be obtained with only one batch.
31/1183-1193	Section IV. Drug Product Characterization Studies, B. Effect on Resting Time	This study should be based on the minimum number of actuations specified in the labeling.

Please feel free to contact me at 908-740-5680, if you have any questions in this regard.

Sincerely,

Nicholas J. Pelliccione, Ph.D.
Senior Director, CMC
Worldwide Regulatory Affairs

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